

APPLICANT: Stanley T. Crooke
SERIAL NO: 09/479,783

DOCKET NO: ISIS-4313

REMARKS

Claims 78-81, 93-95, 97, 106, 117-140, 147-152 and 176-193 were pending. Upon entry of this Amendment, claims 81, 93, 106 and 176-243 will be pending. Claims 78-80, 94, 95, 97, 117-140 and 147-152 are canceled, claims 81, 93, 106, 179, 186 and 189-192 are amended and new claims 194-243 are submitted herein.

Claims 81 and 93, which were indicated as allowed in the Office Action mailed June 8, 2006, are rewritten as independent claims, incorporating the limitations of claim 78.

Claims 81 and 93 further replace the phrase "make them resistant" with the phrase "increase their resistance" for clarity. Claim 106 is similarly amended. Claims 179 and 186 are amended to correct an inadvertent typographical error such that "2'-O-methoxyethoxy" now reads "2'-O-methoxyethyl," basis for which can be found, for example, at pages 8, 22 and 33 of the specification. Claims 189-192 are amended to replace "nucleobase" with "nucleoside" for proper antecedent basis. Claim 192 is further amended to depend from claim 191 for proper antecedent basis. New claims 194-243 find basis throughout the specification and claims as originally filed. For example, support for the modifications listed in claims 195-201, 205-211, 215-221, 226-232 and 235-241 can be found in the original claims and on pages 7-11 and 22-25 of the specification. Support for oligonucleotide length limitations recited in claims 194, 204, 212, 213, 214, 222, 223, 225 and 234, can be found, for example, at pages 7, 24 and 93 of the specification and in the original claims. Basis for claims 203 and 243 can be found, for example, in Table 1 on page 93 of the specification. Table 1 shows an example of a double-stranded RNA with 17 contiguous nucleotides which are 100% complementary to each other.

New claim 194 incorporates the limitations of now cancelled claims 95 and 140 and further specifies *both* oligonucleotides are independently 15 to 25 nucleoside subunits in length. New claim 204 incorporates the limitations of now cancelled claim 95 and further requires *each* oligonucleotide to comprise at least one modification. New claim 214 incorporates the limitations of cancelled claim 95 and further specifies that the first and second oligonucleotides are 100% complementary to each other. New claim 225 is similar in scope to allowed claim 182, but recites that at least one of the oligonucleotides comprises "at least one chemical modification". In addition, each new independent claim (claims 194, 204, 214, 225 and 234) recites that the chemical modification or modifications can increase

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resistance to single-stranded nucleases or increase affinity of the oligonucleotides for each other. In regard to claim 234, support for oligonucleotides comprising "a plurality of nucleoside subunits with 2'-hydroxyl pentofuranosyl sugar moieties" can be found, for example, on pages 12 and 13 of the specification and in the original claims. No new matter has been added to the claims.

The specification is amended to correct inadvertent typographical and spelling errors. The amendment to Table 1 correctly identifies each oligonucleotide as having a 5' end and a 3' end. In addition, page 1 of the specification is amended to insert reference to U.S. Serial Number 08/870,608, filed June 6, 1997, to which the instant application claims priority as a divisional. Applicant properly claimed priority to the aforementioned application at the time of filing and requested entry of an amendment to insert the claim to priority under the "Cross-Reference to Related Applications" section; however, the published application and filing receipt do not reflect that this amendment has been made. No new matter has been added to the specification.

The claim amendments and cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant reserves the right to file subsequent applications claiming the canceled subject matter.

REJECTION UNDER 35 U.S.C. §102(e)

Claims 78-80, 94, 95, 97, 117-119, 121-125, 127-131, 133-137, 139, 140, 147-149, 151 and 152 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Usman *et al.* (US 6,849,729). The Office Action alleges Usman *et al.* disclose a non-covalently linked double stranded RNA comprised of a synthetic RNA ribozyme and a synthetic RNA substrate. The Office Action further states the compounds have at least four consecutive ribofuranosyl residues with phosphodiester linkages and one strand (the RNA ribozyme) is modified, including 2'-methoxy, 2'-fluoro and phosphorothioate modifications. Applicant respectfully traverses this rejection.

Pending claims

Each of the rejected claims are canceled herein, rendering the rejection moot against these claims. However, new independent claims 194, 204 and 214 incorporate the limitations of canceled claim 95 and/or claim 140. The new claims also specify the chemical

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modification or modifications can include those that increase affinity of one oligonucleotide for the other. Therefore, claims 194, 204 and 214, and all claims depending therefrom, each specify a composition comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein the oligonucleotides are not covalently linked; each oligonucleotide comprises a portion with at least four consecutive ribofuranosyl residues which are base-paired with each other in the duplex; and at least one oligonucleotide comprises at least one chemical modification that increases its resistance to single-stranded nucleases or increases its affinity for the other oligonucleotide. Claim 194 further requires that each oligonucleotide is 15 to 25 nucleoside subunits in length. Claim 204 specifies that each oligonucleotide is 8 to 50 nucleoside subunits in length and *each* oligonucleotide comprises at least one chemical modification. Claim 214 is limited to compositions wherein each oligonucleotide is 8 to 50 nucleoside subunits in length and the oligonucleotides are 100% complementary to each other.

New claims depending from claims 194, 204 and 214 further specify the compositions have at least one modified internucleoside linkage, modified sugar moiety or modified nucleobase (claims 195, 205 and 215); at least one phosphorothioate linkage (claims 196, 206 and 216); at least one 2'-substituted sugar modification (claims 197, 207 and 217); at least one 2'-alkoxy sugar modification (claims 198, 208 and 218); at least one 2'-methoxy modification (claims 199, 209 and 219); at least one 2'-fluoro modification (claims 200, 210 and 220); or at least one 2'-O-methoxyethyl modification (claims 201, 211 and 221). Claims 202 and 224 further limit claims 194 and 214, respectively, to compositions wherein *each* oligonucleotide comprises at least one chemical modification. Claim 203 further limits claim 194 to a composition wherein the first and second oligonucleotide comprise at least 17 contiguous nucleotides which are 100% complementary to each other. Claims 212, 213, 222 and 223 further limit claim 204 or claim 214 to compositions wherein at least one oligonucleotide is 12 to 30, or 15 to 25, nucleoside subunits in length.

The cited reference does not anticipate the pending claims

In order to anticipate a claim, the prior art must teach each and every limitation of the claim. Applicant respectfully submits Usman *et al.* do not teach every element set forth in the pending claims. Usman *et al.* disclose an RNA ribozyme optionally comprising modified nucleotides hybridized to a substrate RNA. The substrate RNAs disclosed by Usman *et al.* are

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not modified. Preferred ribozymes are described by Usman *et al.* as being 30-40 nucleotides in length (see column 7, lines 30-34) and the ribozymes illustrated in Figures 1, 7, 11, 12, 16 and 17 are either 28, 32 or 34 nucleotides in length. The disclosed ribozymes have loop regions which do not hybridize to the RNA substrate and thus are not 100% complementary to the substrate RNA, nor do they have at least 17 contiguous nucleotides which are 100% complementary to the substrate RNA. Therefore, the pending claims are not anticipated because Usman *et al.* do not teach (i) a composition comprising a double stranded RNA wherein each oligonucleotide is 15 to 25 nucleoside subunits in length (claims 194-203); (ii) a composition comprising a double stranded RNA wherein each oligonucleotide comprises at least one chemical modification (claims 204-213); or (iii) a composition comprising a double stranded RNA wherein the first oligonucleotide is 100% complementary to the second oligonucleotide (claims 214-224).

Conclusion

Usman *et al.* do not teach each and every element recited in the instant claims, thus the pending claims are not anticipated. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §102(e).

REJECTION UNDER 35 U.S.C. §103

Claims 120, 126, 132, 138 and 150 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Usman *et al.* (US 6,849,726). The Office Action alleges that although Usman *et al.* do not specifically teach 2'-O-methoxyethoxy modifications, the reference does teach that oligonucleotide modifications are routine matters of choice in the art and methoxy and ethoxy are well known in the art as optional substituents. The Office Action concludes the invention as a whole would have been *prima facie* obvious. Applicant respectfully traverses this rejection.

Claims 120, 126, 132, 138 and 150 are canceled herein, rendering the rejection moot as it pertains to these claims. The new pending claims are described above.

In order to establish a *prima facie* case of obvious, the cited art must teach or suggest each claim limitation. For the reasons stated above in response to the rejection under 35 U.S.C. §102(e), Usman *et al.* do not teach or suggest each and every limitation of the pending claims. Specifically, Usman *et al.* do not teach or suggest (i) a composition comprising a

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SERIAL NO: 09/479,783

DOCKET NO: ISIS-4313

double stranded RNA wherein each oligonucleotide is 15 to 25 nucleoside subunits in length (claims 194-203); (ii) a composition comprising a double stranded RNA wherein each oligonucleotide comprises at least one chemical modification (claims 204-213); or (iii) a composition comprising a double stranded RNA wherein the first oligonucleotide is 100% complementary to the second oligonucleotide (claims 214-224). In fact, Usman *et al.* teach away from these limitations since (i) ribozymes require a certain minimum length (Usman *et al.* teach the length must be at least 28 or 30 nucleoside subunits in length) in order to hybridize to and elicit cleavage of a target RNA; (ii) the substrate RNA represents a cellular target RNA, which would not be modified; (iii) and ribozymes necessarily comprise a loop region which is not 100% complementary to its substrate RNA.

Applicant respectfully submits Usman *et al.* do not teach or even suggest each and every limitation of the pending claims, thus the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a).

ALLOWED CLAIMS

Applicant notes claims 81, 93, 106 and 176-193 were indicated as allowed in the Office Action mailed June 8, 2006. Claims 81 and 93 are herein rewritten as independent claims, incorporating the limitations of claim 78. Applicant respectfully submits claims 81, 93, 106 and 176-193 remain in condition for allowance.

It is believed that no fee is due with this response. However, if a fee is due, the Commissioner is hereby entitled to charge the fee to Deposit Account 50-0252, referencing the above named application.

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss any outstanding matters.

Respectfully submitted,

APPLICANT: Stanley T. Crooke
SERIAL NO: 09/479,783

DOCKET NO: ISIS-4313


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